Minutes of Meeting

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee

May 24, 2006

Attendees: Dr. A. Z. Holloway, Chair; Dr. Mark Carpenter, Dr. Lucy Culpepper, Mr. David Calabrese, Dr. Nan Ferris, Dr. Richard Freeman, Dr. W. Thomas Geary, Ms. Kelli Littlejohn, Mr. Ben Main, Dr. Mary McIntyre, Dr. Lucian Newman, III, and Dr. Kalindi Raval

Absent: Ms. Sheri Lynn Boston and Mr. Dane Yarbrough

1. **OPENING REMARKS**
   Chairman Holloway called the Pharmacy and Therapeutics (P&T) Committee Meeting to order at 9:10 a.m.

2. **APPROVAL OF MINUTES**
   Chairman Holloway asked if there were any corrections to the minutes from the February 22, 2006 P&T Committee Meeting. Since there were no corrections, a motion was made and seconded to approve the minutes.

3. **OLD BUSINESS**
   Medical costs and preferred drug lists
   Mark Carpenter, Ph.D., Director of Statistics at Auburn University, presented a statistical evaluation of the impact of implementation of the Preferred Drug List (PDL) on overall medical costs, which include pharmacy costs. Charts noting the total medical costs per month for 17 therapeutic classes and the statistical significance of any changes were included in the P&T Committee Members' clinical packets. All recipients, with the exclusion of the dually eligible members, who received a prescription for a PDL drug within the specific drug class, were included in the analyses. A p-value <0.05 indicated a statistically significant change in growth rate from pre- and post-implementation of the PDL. From May 2003 through June 2005, there was a significant reduction in growth rate for total medical costs for seven drug classes after implementation of the PDL. There was no significant change in growth rate for total medical costs for 10 therapeutic classes. Dr. Carpenter noted that the costs were not adjusted for inflation.

   Dr. Newman inquired how the growth rates compare to other Medicaid or private insurance programs. Ms. Littlejohn noted that other Medicaid pharmacy programs have reported annual growth rates of 17%-20%. With implementation of the PDL, the Alabama Medicaid Pharmacy Program has experienced a growth of only 2%-4%, while not incurring additional medical costs (directly related to implementation of the PDL).

   Dose simplification
   Dr. Ferris noted that over the past several years, there has been an influx of products brought to the market as either combinations of already available generic medications or as once-daily formulations. P&T Committee Members are asked to evaluate whether these new products offer significant clinical advantages over the generics and other brand products within the same class. The review on dose simplification was originally presented in August 2004. Since that time, the "Effectiveness" section of each new drug and therapeutic class review has been expanded to include studies that have evaluated simplification of therapy

(e.g., combination products, once-daily formulations) and whether administration of these products resulted in better clinical outcomes.

In general, studies have shown that the greatest benefit on adherence from dose simplification may be from moving QID regimens to QD or BID dosing regimens, or in moving from TID to QD dosing regimens. Studies that have compared compliance with BID to TID and QD to BID have not shown consistent results. Dr. Ferris noted that one study reported more 24-hour periods without any medications with the once-daily regimens as compared to twice-daily regimens.

Only a few studies have evaluated the impact of dose simplification on clinical outcomes. One study reported an association between compliance and blood pressure control. The authors noted higher compliance among those taking one antihypertensive tablet per day; however, overall compliance was found in only 15% of patients, with satisfactory blood pressure control documented in only 20% of treated hypertensives. Several studies reported comparable clinical endpoints achieved with a combination product when compared to administration of the individual components. Combination products have not been shown to be safer or more efficacious than administration of the individual components. Combination products are generally not recommended as first-line therapy for the initial treatment of a disease. Additional studies are needed to further clarify the clinical benefits of dose simplification.

Mr. Main inquired if there were any additional studies evaluating patient compliance in rural Medicaid populations. Dr. McIntyre mentioned that some compliance studies incorporate education level and income within the scope of the study. These studies found that the more educated patients had a higher compliance rate.

An article (Arch Intern Med. 2006;166:332-7) that evaluated adherence to chronic therapy in patients enrolled in a 3-tier pharmacy benefit plan was distributed to the P&T Committee Members. Dr. Ferris noted that through an analysis of pharmacy claims, the authors found that adherence was higher for patients initiated on generic medications and preferred medications than with nonpreferred medications.

Dr. Newman asked if there were any explanations for the results. Ms. Littlejohn noted that in the comment section of the article, the authors noted that physician workload may be decreased when more generics are prescribed and pharmacists may play a role in educating patients and facilitating switches.

4. PHARMACY PROGRAM UPDATE

Ms. Littlejohn updated the P&T Committee Members on the uncompensated care reimbursement. The Medicaid Agency will reimburse providers who provided medications, services, supplies and equipment to patients who were not covered by any other insurance or program. More information and instructions about the reimbursement program are on the website. All claims for the uncompensated care must be received by the Medicaid Agency no later than June 30, 2006.

The Agency has a new program available for pharmacy enrollment for Part B Medicare clients. Medicare does cover certain prescription drugs under Part B with J Codes (e.g., hemophilia drugs, clotting factors, immunosuppressives). For more information please refer to the Agency's website. If the pharmacy provider wants to bill Medicaid for Medicare Part B cross over clients, they will need to complete another enrollment application for these cross over clients.

The Commissioner and other Agency clinical staff are currently conducting Medicaid Town Hall Meetings. For more information about meeting dates and times, please refer to the Agency's website. The next PDL quarterly update will be August 1, 2006.

Ms. Littlejohn thanked the P&T Committee Members for their extra efforts in reviewing the large clinical packet for this meeting. She noted that the Agency is legislatively bound to re-review the therapeutic classes in a timely manner. The August meeting will encompass fewer therapeutic classes, and will focus on the antidiabetic agents and estrogen products.

5. ORAL PRESENTATIONS BY MANUFACTURERS/MANUFACTURERS' REPRESENTATIVES

Five-minute verbal presentations were made on behalf of some pharmaceutical manufacturers. Ms. Littlejohn explained the process and timing system for the manufacturers' oral presentations. The drugs and corresponding manufacturers are listed below with the appropriate therapeutic class. There were a total of 11 manufacturers' presentations at the meeting.

6. PHARMACOTHERAPY REVIEWS/RE-REVIEWS (Refer to the web for full text reviews)

The pharmacotherapy reviews began at approximately 9:30 a.m.

Central α-Agonists Single Entity Agents AHFS 240816

Manufacturer comments on behalf of these products:

None

Dr. Raval noted that the central α-agonist agents were previously reviewed in December 2003, and no new agents or formulations have been added to the market since that review. Dr. Raval pointed out that Table 1 indicates what generic and brand products are currently on the Alabama Medicaid PDL. The Appendix of the clinical packet contains a more comprehensive overview of the treatment of the conditions discussed in these pharmacotherapeutic reviews.

Dr. Raval mentioned that national and international guidelines generally do not consider central α-agonists as first-line therapy for hypertension due to their relatively high incidence of side effects, such as dry mouth and sedation. These agents also carry a risk of rebound hypertension following sudden discontinuation of therapy. However, methyldopa is considered a drug of choice for the treatment of chronic hypertension during pregnancy based on long-term follow up studies supporting safety in the fetus.

There have been no significant changes in the pharmacokinetics, drug interaction, or adverse drug event sections since the previous review. These agents are generally accepted to be effective antihypertensive agents in combination with first-line therapies. However, there are limited comparative trials regarding the single entity central α-agonists. A study by Lilja et al. reported that both transdermal and oral clonidine significantly reduced blood pressure compared to placebo, and that there were no differences in the primary endpoints of blood pressure and heart rate between these formulations.

In conclusion, the available data demonstrates comparable safety and efficacy amongst the single entity central α-agonists. The clonidine patch is not available generically. The available data fails to demonstrate enhanced efficacy of one route over another for oral and transdermal clonidine. Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter

(OTC) products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand single entity central α-agonist was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Central α-Agonists Combination Agents AHFS 240816
Manufacturer comments on behalf of these products:
None

Dr. Raval noted that no new agents or formulations have been added to the market since the previous review. Dr. Raval mentioned that the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) guidelines recommend thiazide diuretics as first-line therapy for patients with uncomplicated hypertension. Although central α-agonists are not considered first-line therapy for hypertension, these agents may be used as add-on therapy. The combination agents are comprised of a thiazide diuretic and a central α-agonist.

Dr. Raval pointed out that there have been no significant changes in the pharmacokinetics, drug interaction, or adverse drug event sections since the previous review. The combination agents share the same pharmacology and pharmacokinetics profile as their individual components. She noted that there are limited comparative trials regarding the combination central α-agonists. These agents have been shown to be more effective than monotherapy and/or placebo.

In conclusion, central α –agonists are not recommended as initial therapy of hypertension primarily due to their side effect profile and potential for severe rebound hypertension upon rapid withdrawal of the medication. These agents are used in combination with diuretics, which may allow lower doses to be used for either or both drugs. However, for those patients requiring combination therapy for hypertension management, there are other agents from other antihypertensive categories that are better tolerated. Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand combination central α-agonist was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Direct Vasodilators Single Entity Agents AHFS 240820
Manufacturer comments on behalf of these products:
None

Dr. Ferris noted that there were three agents within the single entity direct vasodilator class. Hydralazine and minoxidil are available generically and are indicated for hypertension. Neither agent is recommended for use as initial therapy and they are rarely used as monotherapy. Oral diazoxide is not available

generically and is indicated for the management of hypoglycemia due to hyperinsulinism in adults due to malignancy. Oral diazoxide is considered a first-line therapy for this condition.

A literature search did not reveal any comparative clinical trials related to the use of diazoxide for the treatment of hypoglycemia secondary to hyperinsulinism. Clinical studies have demonstrated that the single entity direct vasodilators, hydralazine and minoxidil, are efficacious in the treatment of hypertension. There are limited head-to-head trials comparing hydralazine to minoxidil. One study reported greater reductions in diastolic blood pressure with minoxidil than hydralazine; however, minoxidil was associated with more adverse effects. Neither of these agents is considered first-line and they are usually added to existing multidrug antihypertensive regimens when blood pressure is inadequately controlled with other drugs. The direct vasodilators are associated with a number of potentially severe adverse effects, which limits their use. Some of these adverse effects result from a compensatory cardiovascular response (e.g., tachycardia, fluid retention) and may be counterbalanced with other medications, such as β-adrenergic blocking agents and diuretics. Overall, the available data demonstrates comparable safety and efficacy amongst the direct vasodilators. Therefore, all brand products of hydralazine and minoxidil are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

In light of its limited labeled indication, Dr. Ferris recommended that oral diazoxide be managed through the existing medical justification portion of the prior-authorization process. Therefore, oral diazoxide does not offer a significant clinical advantage in general use over the other brands, generics and OTC products in this class.

No brand single entity hydralazine or minoxidil was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. No brand oral diazoxide was recommended for preferred status, regardless of cost. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Direct Vasodilators Combination Agents AHFS 240820
Manufacturer comments on behalf of these products:
BiDil® (isosorbide dinitrate and hydralazine) - NitroMed, Inc.

Dr. Ferris noted that there are currently two direct vasodilator combination agents within this therapeutic class. The product containing hydralazine and hydrochlorothiazide (HCTZ) was available generically and was indicated for the treatment of hypertension. The combination product of hydralazine and isosorbide dinitrate (ISDN) was indicated for the treatment of heart failure as an adjunct to standard therapy in self-identified black patients to improve survival, to prolong time to hospitalization for heart failure, and to improve patient-reported functional status. Dr. Ferris stated that the fixed-dose combination hydralazine and isosorbide dinitrate was not interchangeable with the associated individual components. However, the individual components are available generically in several dosage strengths. Combination products containing reserpine are no longer available.

Dr. Ferris noted that the national guidelines do not recommend the combination vasodilators for the initial treatment of hypertension. For the management of heart failure, the combination of ISDN and hydralazine is reasonable and effective in black patients with New York Heart Association (NYHA) III-IV heart failure,

in addition to standard therapy of angiotensin-converting enzyme (ACE) inhibitor and β-adrenergic blocking agents. She stated that this was a Class IIA recommendation [from the American College of Cardiology/American Heart Association (ACC/AHA) 2005 guidelines]. Dr. Ferris also noted that the ACC/AHA guidelines state that the addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced left ventricular ejection fraction (LVEF) who are already taking an ACE inhibitor and β-adrenergic blocking agent for symptomatic heart failure (HF) and who have persistent symptoms. The guidelines do not specifically state that you need the combination product.

Key pivotal studies within the effectiveness section were discussed. The V-HeFT I trial noted no significant difference in mortality between hydralazine and ISDN versus placebo in men with heart failure, but upon subgroup analysis, a significant mortality reduction with the two agents was observed in black patients. In the V-HeFT II trial, a significantly lower mortality was observed with enalapril compared to hydralazine and ISDN; however, there was no difference between the two treatment groups for the black population. Both of these trials were conducted using the individual agents of hydralazine and ISDN administered concurrently, and the results of these two retrospective analyses served as the impetus for the A-HeFT trial, which used the fixed-dose combination product. The A-HeFT trial was conducted in patients with stable symptomatic heart failure. The trial was terminated early because the primary endpoint of composite score was statistically better with the combination product. There was a 43% decrease in all-cause mortality and a 39% reduced risk reduction in first hospitalization compared to placebo.

Dr. Ferris concluded there was very limited data regarding the combination product hydralazine and HCTZ. This product was not considered a first-line therapy and was reserved for use in patients who have shown an inadequate response to monotherapy. As noted in the clinical studies, the hydralazine and ISDN combination has proven to be beneficial in the treatment of heart failure in black patients. Dr. Ferris noted that the individual components of this medication are available generically. Although the individual components are not interchangeable with the fixed-dose combination product, there are several dosage strengths available, which allows for adequate titration to reach desired clinical benefit. Clinical studies have demonstrated clinical benefit with hydralazine and ISDN in dosages achievable through concomitant use of the individual components.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer not significant clinical advantage over other alternatives in general use.

No brand combination direct vasodilator was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Dr. Geary inquired if there were any studies comparing administration of the individual components to that of the fixed-dose combination product. Dr. Ferris replied that there were not any studies at this time. Dr. Holloway asked if the ACC/AHA 2005 guidelines specifically recommend the fixed-dose combination product. Dr. Ferris replied that the guidelines did not specifically state the fixed-dose combination product but recommended the "addition of hydralazine and ISDN" within the special population section (ACC/AHA 2005 page 1845) and "a combination of hydralazine and a nitrate" for patients with reduced LVEF (ACC/AHA 2005 page 1837). There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Peripheral Adrenergic Inhibitors Single Entity Agents AHFS 240832
Manufacturer comments on behalf of these products:
None

Dr. Ferris stated that reserpine was the only single entity peripheral adrenergic inhibitor that was still on the market. It was available generically and was on the PDL. In the JNC 7 guidelines for the treatment of hypertension, reserpine was listed as a treatment option, either alone or in combination with a diuretic, but it was not recommended first line.

Most of the clinical studies evaluated the efficacy of reserpine in lowering blood pressure in patients already on a diuretic. Reserpine produced additional benefit when added to diuretic therapy and lower doses of reserpine were required with the two agents. When combined with diuretics, reserpine achieved blood pressure control comparable to diuretics plus β-adrenergic blocking agents, calcium-channel blocking agents or methyldopa. While clinical studies demonstrated that reserpine was effective in reducing blood pressure; due to its side effect profile, it was not used as a first-line agent. Dr. Ferris noted that reserpine was rarely used as monotherapy for the treatment of hypertension, but as adjunctive therapy, and in low dose combinations with thiazide diuretics.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand peripheral adrenergic inhibitor was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Hypotensive Agents, Miscellaneous Single Entity Agents AHFS 240892
Manufacturer comments on behalf of these products:
None

Dr. Ferris pointed out that mecamylamine was the only agent in this class. Mecamylamine was indicated for moderately severe to severe essential hypertension and for uncomplicated malignant hypertension.
It was not available generically and was not on the PDL. The national and international guidelines for hypertension do not address mecamylamine as a treatment option.

The most common side effects reported with mecamylamine include orthostatic dizziness, postural hypotension, constipation, dryness of mouth, nausea, vomiting, fatigue and sedation. A search of Medline and Ovid did not reveal any clinical trials measuring the safety or efficacy of mecamylamine for the treatment of hypertension. The initial clinical trials were conducted in the 1950s. Micromedex stated that mecamylamine was effective for these conditions and should only be considered as a supplementary agent after first-line antihypertensive agents have failed to be effective.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand single entity miscellaneous hypotensive agent was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Alpha-Adrenergic Blocking Agents Single Entity Agents AHFS 242000
Manufacturer comments on behalf of these products:
None

Dr. Ferris noted that the no new agents or formulations have been added to the market since the previous review. All three single entity α-adrenergic blocking agents are available generically and are indicated for the treatment of hypertension and benign prostatic hyperplasia (BPH). There have been no significant changes in the pharmacokinetics, drug interaction, or adverse drug event sections since the previous review.

Key pivotal trials were discussed. Overall, the α-adrenergic blocking agents have been shown to be significantly more efficacious than placebo and comparable to other classes of antihypertensive agents in reducing blood pressure. The ALLHAT study compared the effects on cardiovascular morbidity and mortality of the α-adrenergic blocking agents to other classes of antihypertensive drugs. Doxazosin was found to be associated with a higher risk of stroke, combined cardiovascular disease and congestive heart failure than chlorthalidone. Due to results from the ALLHAT trial, the role of the α-adrenergic blocking agents in the management of hypertension and BPH have been challenged. There was no evidence that demonstrated that one α-adrenergic blocking agent was safer or more efficacious than the others for the treatment of hypertension or BPH.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand α-adrenergic blocking agent was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possible designate one or more preferred brands. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Alpha-Adrenergic Blocking Agents Combination Agents AHFS 242000
Manufacturer comments on behalf of these products:
None

Dr. Ferris stated that the combination product of prazosin and polythiazide was the only agent included in this review and it was not available generically. The combination product was indicated for the treatment of hypertension. The national guidelines for the management of hypertension do not recommend an α-adrenergic blocking agent as initial therapy.

The combination product of prazosin and polythiazide shares the same pharmacokinetics, drug interactions, and adverse events as its individual components. There are limited comparative trials regarding the combination α-adrenergic blocking agents. In open-labeled studies, the prazosin and polythiazide combination was effective in reducing blood pressure and the two agents were more effective than monotherapy. There are no studies that have shown that the combination product reduces cardiovascular morbidity and mortality. Due to results of the ALLHAT study, the role of the α-adrenergic blocking agents

has been challenged and the use of this combination product is limited.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand combination α-adrenergic blocking agent was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Beta-Adrenergic Blocking Agents Single Entity Agents AHFS 242400
Manufacturer comments on behalf of these products:
Toprol-XL® (metoprolol succinate extended-release) - AstraZeneca

Dr. Ferris began her presentation by noting that most of the single entity β-adrenergic blocking agents were available generically and were on the PDL. The indications and role of these agents for the management of hypertension, heart failure, myocardial infarction and angina were discussed. There have been no significant changes in the pharmacokinetics, drug interaction, or adverse drug event sections since the previous review.

Key pivotal trials were discussed. When administered at effective doses, the β-adrenergic blocking agents produced clinically relevant blood pressure reductions in hypertensive patients. The antihypertensive efficacy and the side effect profiles amongst the different agents do not consistently demonstrate a clinical advantage of one β-adrenergic blocking agent versus another. Beta-adrenergic blocking agents have been shown to reduce morbidity and mortality from heart failure and other comorbid cardiovascular conditions.

Based upon the outcomes from clinical trials (e.g., CIBIS II, MERIT-HF, COPERNICUS, CAPRICORN), the ACC/AHA 2005 guidelines for the management of heart failure recommend bisoprolol, carvedilol or sustained-release metoprolol because these agents have been proven to reduce mortality. Carvedilol and sustained-release metoprolol are the only β-adrenergic blocking agents with an FDA-approved indication for the treatment of heart failure. Bisoprolol is available generically. While carvedilol has been the most extensively studied, there are no head-to-head trials that demonstrate that one of these β-adrenergic blocking agents offers a significant clinical advantage over another for the management of heart failure.

No brand single entity β-adrenergic blocking agent was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Dr. Geary asked "Don't we have one branded agent already on the PDL?" Dr. Ferris replied "Right, Coreg®." Dr. Geary inquired "Essentially is this a recommendation we change that?" Ms. Littlejohn replied, "No sir. Coreg® is on the PDL in a supplemental rebate contract, so that would not be involved at this time." There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Comment: Can't this change based on quarterly updates? I understood her to say that there were no plans to change "at this time" but this is based on PDL updates. PLEASE VERIFY the exact wording. This could come back to bite us. Mgm

Beta-Adrenergic Blocking Agents Combination Agents AHFS 242400
Manufacturer comments on behalf of these products:
None

Dr. Ferris noted that there were six combination β-adrenergic blocking agents and four were available generically. They all combine a β-adrenergic blocking agent with a diuretic and are indicated for the treatment of hypertension. The combination agents share the same pharmacokinetics, drug interactions, and adverse reaction profiles as their individual components.

She noted that there are limited comparative trials regarding the combination β-adrenergic blocking agents. These agents have been shown to be more effective than monotherapy and/or placebo, and comparable to agents from other therapeutic classes. One study reported comparable efficacy when atenolol and chlorthalidone were given as a fixed-dose combination product versus concurrent administration of the individual components.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand combination β-adrenergic blocking agent was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Calcium-Channel Blocking Agents Dihydropyridines Single Entity Agents AHFS 242808
Manufacturer comments on behalf of these products:
None

Dr. Ferris directed the P&T Committee Members to the table that listed all of the single entity dihydropyridine calcium-channel blocking agents included in the review. She mentioned that since the previous review, several new generic formulations have been introduced to the market. All of these agents were indicated for the treatment of hypertension, with the exception of nimodipine, which was indicated for the treatment of subarachnoid hemorrhage. Amlodipine, nicardipine and nifedipine were also indicated for angina. The role of the calcium-channel blocking agents in the management of hypertension and angina was discussed.

Minor differences were noted among the pharmacokinetics, drug interactions and adverse reactions for these agents. With the exception of nimodipine and nicardipine, all of the dihydropyridines are available in a once-daily formulation. In the clinical trials, the dihydropyridine calcium-channel blocking agents have demonstrated efficacy in the management of hypertension, and amlodipine, nicardipine and nifedipine have demonstrated efficacy for angina. In cardiovascular outcome trials, most results reported more favorable outcomes with the comparator therapy (primarily angiotensin-converting enzyme inhibitors and diuretics) as opposed to the dihydropyridine. The ASCOT-BPLA found more favorable cardiovascular outcomes with amlodpine when compared to atenolol.

In clinical trials directly comparing one dihydropyridine to another, there is insufficient evidence to demonstrate that one product offered a clear advantage over another dihydropyridine in terms of safety and efficacy. The majority of these trials demonstrated nonsignificant differences in reductions in blood pressure, angina episodes or nitrate use. In most trials that demonstrated significant differences in blood pressure reductions, the differences were small and the clinical impact of the differences were not measured

within the trials. One trial did note a larger and significant decrease in 24-hour systolic pressure with amlodipine compared to nicardipine in patients with isolated systolic hypertension. In terms of compliance and tolerability, one study reported better compliance and another study reported fewer adverse reactions with amlodipine versus felodipine. Amlodipine and isradipine have a low incidence of significant drug-drug interactions.

Based on this information, there was not substantial evidence to conclude that any one brand-name dihydropyridine calcium-channel blocking agent offered a significant clinical advantage in terms of efficacy or safety over all other dihydropyridines. Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand dihydropyridine calcium-channel blocking agent was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Calcium-Channel Blocking Agents, Miscellaneous Single Entity Agents AHFS 242892
Manufacturer comments on behalf of these products:
Cardizem® LA (diltiazem) – Kos Pharm., Inc.

Dr. Ferris directed the P&T Committee Members to the table that listed all of the miscellaneous calcium-channel blocking agents in the review. Since the previous review, a new formulation for diltiazem has become available. Both diltiazem and verapamil are indicated for angina and hypertension; however, the labeled indications vary according to the dosage formulation. The role of these agents in the management of hypertension, angina and myocardial infarction were mentioned.

There have been no significant changes in the pharmacokinetics, drug interaction and adverse event sections since the previous review.

The clinical trials demonstrated the efficacy of the miscellaneous calcium-channel blocking agents in their FDA-approved indications of hypertension, and for selected products, angina. Retrospective analysis of two large cardiovascular outcome trials demonstrated that verapamil and diltiazem reduced mortality and improved cardiovascular outcomes. In post myocardial infarction patients, diltiazem significantly reduced nonfatal cardiac events compared to placebo. There are limited well-controlled trials of adequate size directly comparing diltiazem and verapamil. One small study showed similar increases in time to angina during exercise and total exercise time with diltiazem and verapamil; however, diltiazem significantly reduced weekly angina attacks and nitroglycerin use compared to verapamil.

Currently three branded miscellaneous calcium-channel blocking agents are available in controlled-onset or graded-release formulations. When dosed nightly, the release matrix ensures maximum effect is seen during the waking hours, when the rate of acute myocardial infarction, stroke and cardiovascular death is increased. In clinical trials, these agents have shown significant reductions in blood pressure and heart rate; however, the clinical significance of this early morning protection has yet to be determined. In the large-scale CONVINCE study, controlled-onset verapamil failed to demonstrate equivalence to atenolol or HCTZ in

preventing cardiovascular disease-related events. Additionally, there was no difference in the incidence of cardiovascular disease-related events in the hours from 6 a.m. to noon.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand miscellaneous calcium-channel blocking agent was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Dr. Holloway asked Dr. Geary about the importance of lowering blood pressure in the early morning. Dr. Geary responded that he was not aware of any compelling evidence to suggest positive outcomes related to blood pressure lowering in the early morning. He stated that there does seem to be a higher incidence of myocardial infarction and stroke in the early morning hours; however, cardiologists are not dosing long-acting nitrates to cover early morning hours. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Angiotensin-Converting Enzyme Inhibitors Single Entity Agents AHFS 243204
Manufacturer comments on behalf of these products:
None

Dr. Raval began her presentation by noting that since the previous review, benazepril, fosinopril, and quinapril are now available generically. Dr. Raval noted that the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and the World Health Organization recommends angiotensin-converting enzyme (ACE) inhibitors as first-line options for patients with hypertension complicated by comorbidities, such as cerebrovascular disease, chronic kidney disease, diabetes, heart failure, and myocardial infarction.

The American Diabetes Association recommendations regarding the use of ACE inhibitors or angiotensin receptor blockers in diabetic patients with albuminuria or nephropathy are based on clinical trial data specific to the type of diabetes and degree of renal disease. ACE inhibitors are recommended in hypertensive patients with type 1 diabetes and any degree of albuminuria and in hypertensive type 2 diabetics with microalbuminuria.

There were no significant changes in the pharmacokinetics, drug interaction, or adverse drug event sections since the previous review. Dr. Raval noted that the clinical significance of pharmacokinetic differences between ACE inhibitors remains unclear.

Clinical studies regarding the effectiveness of ACE inhibitors were discussed. The CAMELOT study, conducted in patients with coronary artery disease, showed that both amlodipine and enalapril were significantly better than placebo in reducing cardiovascular events. The study further reported that there was no significant difference between amlodipine and enalapril for the incidence of cardiovascular events. The HOPE study, also conducted in patients with coronary artery disease, found that ramipril was significantly better compared to placebo in reducing the risk of death from cardiovascular causes. The ELITE II trial found no significant difference in all-cause mortality between losartan and captopril in hypertensive patients with heart failure.

In conclusion, ACE inhibitors have a place in therapy for several cardiovascular conditions. However, limited studies of appropriate dosages and of adequate duration have been conducted comparing ACE inhibitor agents to one another. Overall, no one ACE inhibitor offers a significant clinical advantage over another. Therefore, all brand products within the class reviewed are comparable to each other and to the generic and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand single entity angiotensin-converting enzyme inhibitor was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Angiotensin-Converting Enzyme Inhibitors Combination Agents AHFS 243204
Manufacturer comments on behalf of these products:
None

Dr. Raval noted the combination angiotensin-converting enzyme (ACE) inhibitors were previously reviewed in August of 2003 and that all single entity ACE inhibitors are available in combination with a diuretic or a calcium channel blocking agent, with the exception of perindopril and ramipril. All of the combination ACE inhibitors are FDA approved solely for hypertension and the combination products have similar pharmacokinetic, drug interaction, and adverse event profiles as their individual components.

Clinical studies within the effectiveness section were discussed. All ACE inhibitors have been documented to be efficacious in lowering blood pressure. Several studies demonstrated additional benefit in blood pressure lowering with the combination ACE inhibitor products compared to either agent alone. However, few studies directly compared one combination ACE inhibitor to another.

In conclusion, combination ACE inhibitor agents are generally not recommended as first-line therapy and are reserved for patients who have had an inadequate response to therapy with the individual agents. Although clinical trials show improvements in blood pressure control when additional antihypertensive agents are added, there is not enough evidence to conclude that combination products are significantly more effective than administration of the separate components.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand combination angiotensin-converting enzyme inhibitor was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Angiotensin II Receptor Antagonists Single Entity AHFS 243208
Manufacturer comments on behalf of these products:

Atacand® (candesartan) - AstraZeneca
Avapro® (irbesartan) - Bristol Myers Squibb
Cozaar® (losartan) - Merck
Micardis® (telmisartan) - Boehringer Ingelheim

Dr. Raval noted that the single entity angiotensin II receptor antagonists (ARBs) were previously reviewed in August of 2003. Since the previous review no new agents or formulations have become available. Dr. Raval highlighted the current treatment guidelines for the place in therapy of ARBs in patients with heart failure, hypertension, post myocardial infarction, and diabetic nephropathy. Dr. Raval also noted there have been no significant changes in the pharmacokinetics, drug interaction, or adverse drug event sections.

Clinical studies measuring effectiveness were discussed. The PREVAIL trial was a meta-analysis of 43 randomized, placebo-controlled trials that found comparable antihypertensive efficacy of losartan, valsartan, irbesartan, and candesartan when administered at their recommended doses. The Val-HeFT trial concluded that compared to placebo, valsartan resulted in a significant decrease in heart failure hospitalizations and the composite endpoint of morbidity and mortality. The CHARM-Added trial found that adding candesartan 32 mg daily to an ACE inhibitor led to a significant reduction in the relative risk for the primary endpoint of cardiovascular death and heart failure hospitalization. The ELITE II trial found no significant difference between losartan and captopril in all-cause mortality in an elderly population with heart failure and no history of an ACE inhibitor. A meta-analysis of 24 trials by Lee et al. found that ARBs were associated with reduced all-cause mortality and reduced heart failure hospitalizations in patients with chronic heart failure.

Dr. Raval concluded that all of the ARBs are FDA approved for the treatment of hypertension; however, there are differences among the products regarding approval for other indications. It is still undetermined whether the clinical benefit of ARBs for those indications is product specific or a class effect. Also, comparative data regarding the ARBs has not demonstrated distinct, clinically significant differences regarding safety and tolerability between the agents. Overall, no one ARB offers a significant clinical advantage over another. In addition, more clinical data is available on patient outcomes including morbidity and mortality benefit for ACE inhibitors than for ARBs. Therefore, all brand products within the class reviewed are comparable to each other and to the generic and OTC products in this class, and offer no significant clinical advantage over other alternatives in general use.

No brand angiotensin II receptor antagonist was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Dr. Holloway inquired how the current ARBs on the PDL were determined. Ms. Littlejohn noted that the agents on the PDL were determined based on cost effectiveness comparisons to other therapeutic alternatives and considerations included supplemental rebates. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Addendum to the minutes: Please note that the reference numbers in the clinical packet for this review were corrected.

Angiotensin II Receptor Antagonists Combination Agents AHFS 243208

Manufacturer comments on behalf of these products:
Micardis HCT® (telmisartan and hydrochlorothiazide) - Boehringer Ingelheim
Hyzaar® (losartan and hydrochlorothiazide) - Merck

Dr. Raval noted that all of the single entity ARBs are available in combination with hydrochlorothiazide (HCTZ). All of the combination ARBs are FDA approved solely for hypertension, with the exception of losartan and HCTZ, which is also approved for stroke risk reduction in patients with hypertension and left ventricular hypertrophy. Dr. Raval mentioned that the nationally recognized JNC 7 guidelines recommend using a diuretic as first-line therapy for patients with uncomplicated hypertension. Compelling indications for initial therapy with ARBs in hypertensive patients include heart failure, diabetes, and chronic kidney disease.

The combination products have similar pharmacokinetic, drug interaction, and adverse event profiles as their individual components. Clinical studies regarding the effectiveness section were discussed. All ARBs have been documented to be efficacious in lowering blood pressure. The majority of the studies report no significant therapeutic differences between the ARBs. Studies show an additive response in blood pressure lowering when ARBs are added to HCTZ. The combination ARBs are not considered first-line therapies and are reserved for those patients who have demonstrated an inadequate response to the individual components. Overall, no definitive conclusion exists on the enhanced safety of one agent over another.

Therefore, all brand products within the class reviewed are comparable to each other and to the generic and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand combination angiotensin II receptor blocker was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Mineralocorticoid (Aldosterone) Receptor Antagonists Single Entity AHFS 243220
Manufacturer comments on behalf of these products:
None

Dr. Ferris noted that there are two agents in this class and they include eplerenone and spironolactone. Spironolactone is available generically and is on the PDL. Eplerenone is considered a relatively selective mineralocorticoid receptor antagonist because it has a low affinity for glucocorticoid, progesterone and androgen receptors. Both agents are indicated for the treatment of hypertension and heart failure. Spironolactone has a few additional indications. The JNC 7 recommends aldosterone antagonists as an option for hypertensive patients with comorbidities of post myocardial infarction or heart failure. For the management of heart failure, the aldosterone antagonists are recommended in addition to standard therapy in patients with NYHA class III-IV failure with a reduced LVEF of $\leq$ 35%. Neither of the guidelines recommends one agent over another.

One head-to-head trial comparing eplerenone to spironolactone for the treatment of mild-to-moderate hypertension demonstrated that at all doses, eplerenone and spironolactone were more effective than placebo. Reductions in blood pressure with eplerenone 50 mg BID or 100 mg QD were about 50% and

75%, respectively, than that observed with spironolactone 50 mg BID. The incidence of adverse events was comparable between the eplerenone and spironolactone groups.

Dr. Ferris highlighted two pivotal trials with these agents in the management of heart failure. In the EPHESUS trial, eplerenone added to optimal medical therapy reduced morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure. There were no significant differences between eplerenone and placebo in the incidence of sex hormone related adverse events. In the RALES trial, spironolactone in addition to standard therapy substantially reduced the risk of both morbidity and death among patients with severe heart failure. Gynecomastia or breast pain was reported in 10% of men receiving spironolactone as compared to 1% in the placebo group.

Dr. Ferris concluded that the mineralocorticoid receptor antagonists are safe and effective for the treatment of heart failure and hypertension. For the treatment of heart failure, both agents have been shown to reduce all-cause mortality compared to placebo. There are no large scale head-to-head trials comparing the safety and efficacy of eplerenone and spironolactone for the management of hypertension or heart failure. Compared to placebo, spironolactone has been associated with a higher incidence of sex hormone related adverse events than eplerenone. Eplerenone is extensively metabolized through the CYP 3A4 enzyme system, which increased the potential for drug interactions. Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand mineralocorticoid (aldosterone) receptor antagonist was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Mineralocorticoid (Aldosterone) Receptor Antagonists Combination Agents AHFS 243220
Manufacturer comments on behalf of these products:
None

Dr. Ferris noted that there was one combination mineralocorticoid (aldosterone) receptor antagonist in this class review. The combination product hydrochlorothiazide (HCTZ) and spironolactone was available generically and was on the PDL. She discussed the indications and noted that the manufacturer and national guidelines do not recommend the combination product for initial treatment of hypertension or edema.

The combination product has similar pharmacokinetic, drug interaction, and adverse event profiles as its individual components. Clinical studies within the effectiveness section were discussed. Studies that evaluated the agents alone versus the combination product in mild to moderate hypertension reported effectiveness in all treatment arms. Potassium levels markedly decreased with HCTZ. Spironolactone had a moderate dose-related increase of potassium. There were no studies that have shown that the combination product was more effective than concomitant administration of the individual components.

Dr. Ferris concluded that the combination mineralocorticoid (aldosterone) receptor antagonists do not demonstrate a clinical advantage over the individual components when coadminstered. They are not indicated for initial therapy for the treatment of hypertension or edematous conditions according to the national and international hypertension and heart failure guidelines. Therefore, all brand products within the

class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand combination mineralocorticoid (aldosterone) receptor antagonist was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Diuretics Single Entity AHFS 402800
Manufacturer comments on behalf of these products:
None

Dr. Ferris began the discussion by noting that the diuretic single entity review consists of the loop and thiazide diuretics. She pointed out that there were several generic formulations of the loop and thiazide diuretics. All of the loop diuretics and most of the thiazide diuretics are currently on the Alabama Medicaid PDL. The single entity diuretics are primarily indicated for the treatment of edema and/or hypertension. She noted that most national and international organizations consider the single entity diuretics, specifically thiazide-type diuretics as first-line agents for treating hypertension in patients who do not have other significant comorbid conditions. Single entity diuretics are also indicated in hypertensive patients with compelling comorbidities of heart failure, post myocardial infarction, high coronary disease risk, diabetes and recurrent stroke prevention. The loop diuretics are recommended over the thiazide diuretics with reduced renal function. In regards to heart failure, single entity diuretics are recommended to reduce the signs and symptoms of heart failure. Some national and international organizations endorse thiazide diuretics as the preferred choice in hypertensive heart failure patients with mild fluid retention since they give a more persistent antihypertensive effect, whereas others state loop diuretics are more effective than thiazide diuretics.

There are no significant differences among these agents with regards to pharmacokinetics, drug interactions, adverse events and dosing and administration.

Clinical studies within the effectiveness section were discussed. In general, the loop diuretics demonstrated comparable efficacy to each other for heart failure, edema, and hypertension. The thiazide diuretics demonstrated comparable efficacy to each other for hypertension. Overall comparative studies between a loop diuretic (furosemide) and a thiazide diuretic (HCTZ) demonstrated comparable efficacy. Dr. Ferris also pointed out the results of the ALLHAT trial, which concluded that thiazide type diuretics are more effective in preventing one or more major forms of cardiovascular disease and should be preferred for initial antihypertensive therapy.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand single entity diuretic was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Diuretics Combination AHFS 402800
Manufacturer comments on behalf of these products:
None

Dr. Ferris noted that this review included the fixed-dose combination products of amiloride and hydrochlorothiazide (HCTZ) and triamterene and HCTZ, which are both available generically. Amiloride and triamterene are potassium-sparing diuretics. The guidelines for the treatment of hypertension and heart failure do not have specific recommendations for the use of the combination diuretics. The manufacturers of the fixed-dose combination products do not recommend their use for the initial treatment of hypertension or edema, except in individuals in whom the development of hypokalemia must be avoided. The combination products have similar pharmacokinetic, drug interaction, and adverse event profiles as their individual components and there are no significant differences between the combination products.

Clinical studies within the effectiveness section were discussed. In general, for the treatment of hypertension, the combination products were shown to be more effective than the single entity diuretics. The addition of a potassium-sparing diuretic minimized the loss of potassium with the thiazide diuretic. When the combination products were compared to each other, both treatments demonstrated comparable efficacy in controlling blood pressure. Overall, there were no significant differences in the number of adverse events or laboratory parameters. There are no studies that have demonstrated significant differences in clinical outcomes when the agents were administered separately versus a combination product.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand combination diuretic was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Potassium Sparing Diuretics Single Entity AHFS 402800
Manufacturer comments on behalf of these products:
None

Dr. Ferris pointed out that amiloride was the only potassium-sparing diuretic that was included in this review as spironolactone was evaluated with the mineralocorticoid receptor antagonists. She noted that amiloride was available generically and was on the PDL. Dr. Ferris commented that amiloride was rarely used alone and was indicated for congestive heart failure or hypertension as adjunctive treatment with thiazide diuretics or other kaliuretic diuretics. Amiloride was also indicated for the prevention of hypokalemia in patients at risk of hypokalemia.

Clinical studies demonstrated amiloride was safe and efficacious for the treatment of hypertension, edematous conditions, and preventing serum potassium loss in patients taking thiazide diuretics or loop diuretics. As monotherapy, amiloride was considered a weak antihypertensive; therefore, it was rarely used alone. Dr. Ferris noted that amiloride's primary role was in combination with a loop or thiazide diuretic to provide an additive hypotensive effect, minimize potassium excretion, prevent potassium excretion, and prevent diuretic-induced hypokalemia in patients being treated for hypertension and edematous conditions.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand single entity potassium-sparing diuretic was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

7. NEW DRUG REVIEWS

Asmanex® Twisthaler® (mometasone furoate inhalation powder) AHFS 680400 Adrenals
Manufacturer comments on behalf of these products:
None

Mr. Calabrese began his presentation by noting that mometasone (Asmanex® Twisthaler®) was approved by the Food and Drug Administration (FDA) in March 2005 and was the seventh different inhaled corticosteroid currently on the market. Mometasone was indicated for asthma maintenance therapy in patients aged 12 years and older, and also for treatment in patients requiring oral corticosteroid therapy as a means of potentially decreasing or eliminating the need for oral corticosteroids. Mr. Calabrese noted that mometasone was considered a high potency steroid and compared to other inhaled steroid products, demonstrated one of the lowest rates of systemic bioavailability (<1%). Mr. Calabrese stated that mometasone was available as a dry powder form delivered via a breath-activated device (Twisthaler®) and may be administered once daily, making it one of only two agents (the other being budesonide) with a once-daily indication.

When compared to placebo, mometasone demonstrated statistically significant improvements in primary endpoints [e.g., forced expiratory volume in one second (FEV_1)] as well as a variety of secondary endpoints. In direct comparator trials to other inhaled corticosteroids, including fluticasone, budesonide and beclomethasone, mometasone (typically administered as a BID dosing regimen) proved at least comparable in improving FEV_1, as well as other secondary asthma-related evaluation criteria. Mometasone demonstrated statistically significant advantages over budesonide in primary endpoints in studies comparing BID and QD dosing of each product. Mometasone demonstrated no difference in adrenal suppression compared to fluticasone, but demonstrated less of an impact on serum cortisol levels compared to beclomethasone.

Mr. Calabrese summarized that mometasone furoate dry-powder inhalation was considered an effective new therapy for controlling asthma symptoms, improving pulmonary function and decreasing the use of rescue medications and orally administered corticosteroids. The product was well-tolerated and offered the convenience of a once-daily dosing indication; however, there was no evidence to support improved adherence or compliance with this product. There is no evidence to support the hypothesis that higher potency corticosteroids are more efficacious nor do the current guidelines distinguish specific product selection based upon potency. Based upon the available data, there was no substantial evidence that mometasone was more efficacious or offered a greater degree of safety versus other inhaled corticosteroid products.

No brand inhaled mometasone (Asmanex® Twisthaler®) was recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Byetta® (exenatide) AHFS 682092 Antidiabetic Agents, Miscellaneous
Manufacturer comments on behalf of these products:
Byetta® (exenatide) - Amylin Pharm., Inc.

Mr. Calabrese opened his presentation by stating that exenatide (Byetta®) was FDA approved in April 2005 and belonged to a new class of antidiabetic agents known as the incretin mimetics. He noted that exenatide was indicated as adjunct therapy in type 2 diabetics to improve glycemic control in patients who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, but have not achieved adequate glycemic control. As this time, the role of exenatide in the management of diabetes has not been addressed by any of the prominent diabetes treatment guidelines.

Mr. Calabrese summarized the results of several clinical trials evaluating the efficacy of exenatide. When dosed 5 mcg or 10 mcg subcutaneously BID (which is the manufacturer's recommended dose), exenatide achieved statistically greater reductions in HbA1c (primary endpoint) versus placebo. Exenatide also yielded positive benefits versus placebo on a variety of secondary endpoints, including achievement of HbA1c of <7%, and reduction in fasting and postprandial plasma glucose. In addition, exenatide demonstrated reductions in body weight. When compared to insulin glargine, exenatide produced comparable reductions in HbA1c. Insulin glargine, however, produced greater reductions in fasting blood glucose, while exenatide achieved a more positive impact on body weight. The dropout rate was twice as high with exenatide, primarily due to adverse events.

Mr. Calabrese highlighted the significant adverse events and drug interactions with exenatide. He noted that gastrointestinal tolerability was a concern with over 40% of patients reporting nausea, 13% vomiting and 13% diarrhea in the clinical trials. Hypoglycemia risk did not increase when exenatide was added to metformin. When combined with a sulfonylurea, the incidence of hypoglycemia increased, and thus it is recommended that the dose of a sulfonylurea be decreased when exenatide is added. The safety and efficacy of exenatide has not been established in patients less than 15 years of age. Mr. Calabrese noted that some patients in the clinical trials developed anti-exenatide antibodies. At this point, it did not appear that these antibodies decreased effectiveness or increased safety concerns with the drug; however longer-term clinical trials are needed.

Mr. Calabrese concluded that exenatide offered a unique mechanism of action and demonstrated a positive impact on HbA1c in patients not adequately controlled on oral therapies. Exenatide was associated with a high incidence of gastrointestinal adverse effects, which have led to moderate rates of discontinuation. Given the potential for off-label use as a weight loss treatment, the lack of published long-term safety and efficacy data, and its limited indication as adjunct therapy, Mr. Calabrese recommended that this agent be managed through the existing medical justification portion of the prior-authorization program.

No brand of exenatide (Byetta®) was recommended for preferred status, regardless of cost.

Dr. Newman expressed concerns that this agent be reviewed again as more information becomes available. He noted that his endocrinologists are using it according to the manufacturer's labeling. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

Symlin® (pramlintide) AHFS 682092 Antidiabetic Agents, Miscellaneous
Manufacturer comments on behalf of these products:
Symlin® (pramlintide) - Amylin Pharm., Inc.

Mr. Calabrese stated that pramlintide was a synthetic analog of the human hormone amylin. He noted that pramlintide was indicated in type 1 diabetics as adjunct to mealtime insulin in those not achieving adequate glucose control despite optimal insulin therapy. Pramlintide was also indicated in type 2 diabetics as adjunct to mealtime insulin in patients who have failed to achieve glucose control despite optimal insulin therapy, with or without concurrent oral sulfonylurea medications and/or metformin therapy. Like exenatide, the role of pramlintide in the management of diabetes has not been addressed by any of the prominent diabetes treatment guidelines.

The results of several efficacy trials were presented. When combined with mealtime insulin in either a TID or QID dosing regimen, pramlintide yielded significantly greater reductions in HbA1c versus placebo. Pramlintide also demonstrated positive benefits versus placebo in various secondary endpoints, including the proportion of patients reaching HbA1C goal of <7% and reductions in body weight. Like exenatide, pramlintide is also associated with a high incidence of gastrointestinal intolerance with 48% of patients reporting nausea, 17% anorexia and 11% vomiting. During the clinical trials, pramlintide was associated with a substantially increased risk of serious hypoglycemic events when combined with insulin leading to a "black box" warning advising prescribers of this risk and the importance of appropriate patient selection, and insulin dose adjustments when pramlintide was added. Mr. Calabrese also mentioned conditions whereby the manufacturer does not recommend pramlintide therapy (e.g., poor compliance with insulin or glucose self-monitoring, recurrent severe hypoglycemia requiring assistance in the past 6 months, gastroparesis, pediatric patients). Pramlintide dose needs to be titrated and closely monitored with weekly contact with the healthcare professional until target pramlintide dose was achieved, tolerability was established and blood glucose was stabilized. Pramlintide cannot be mixed with insulin.

Mr. Calabrese concluded that pramlintide provides an additional option for adjunctive therapy in fairly motivated and educated type 1 or type 2 diabetic patients who have not achieved optimal glycemic control despite routine insulin usage. Pramlintide has been associated with a high incidence of gastrointestinal intolerance and carries a significant risk of serious hypoglycemia when combined with insulin. Thus careful patient selection, proper patient education and close physician supervision would be warranted with initiation of pramlintide therapy. Mr. Calabrese also noted that pramlintide was being studied as a weight loss therapy and thus carries some risk for off-label use. In light of all of these factors, Mr. Calabrese recommended that pramlintide be best managed through the existing medical justification portion of the prior-authorization process.

No brand of pramlintide (Symlin®) was recommended for preferred status, regardless of cost. There were no further discussions on the drugs in this class. Chairman Holloway asked the P&T Committee Members to mark their ballots.

8. RESULTS OF VOTE ANNOUNCED

Ms. Littlejohn announced the results of voting for each of the therapeutic classes. Results of voting are described in the Appendix to the minutes.

9. NEW BUSINESS

There was no new business

10. NEXT MEETING DATE

The next P&T Committee Meeting is scheduled for 9:00 a.m. on August 23, 2006.

11. ADJOURN

The meeting was adjourned at 12:26 p.m

Addendum to the minutes: Please note the following correction in the Overview of Acute Myocardial Infarction on page 424 of the May 24, 2006 clinical packet. IV NTG is indicated during the first 48 hours for treatment of persistent ischemia, **hypertension** or congestive heart failure, provided that therapy does not preclude treatment with β-blockers or ACE inhibitors.

Appendix

RESULTS OF THE BALLOTING
Alabama Medicaid Agency
Pharmacy and Therapeutics Committee
May 24, 2006

A. The P&T Committee voted unanimously to approve the recommendation that no brand single entity central α-agonist is recommended for preferred drug status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

B. The P&T Committee voted unanimously to approve the recommendation that no brand combination central α-agonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

C. The P&T Committee voted unanimously to approve the recommendation that no brand single entity hydralazine or minoxidil is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

The P&T Committee voted unanimously to approve the recommendation that no brand oral diazoxide is recommended for preferred status, regardless of cost.

Medical Director ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Deputy Commissioner ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Commissioner ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

D. The P&T Committee voted unanimously to approve the recommendation that no brand combination direct vasodilator is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Deputy Commissioner ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Commissioner ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

E. The P&T Committee voted unanimously to approve the recommendation that no brand peripheral adrenergic inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Deputy Commissioner ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Commissioner ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

F. The P&T Committee voted unanimously to approve the recommendation that no brand single entity miscellaneous hypotensive agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

G. The P&T Committee voted unanimously to approve the recommendation that no brand single entity α-adrenergic blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

H. The P&T Committee voted unanimously to approve the recommendation that no brand α-adrenergic blocking agent combination product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

I. The P&T Committee voted unanimously to approve the recommendation that no brand single entity β-adrenergic blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

J. The P&T Committee voted unanimously to approve the recommendation that no brand combination β-adrenergic blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

K. The P&T Committee voted unanimously to approve the recommendation that no brand dihydropyridine calcium-channel blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

L. The P&T Committee voted unanimously to approve the recommendation that no brand miscellaneous calcium-channel blocking agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Deputy Commissioner	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Commissioner	☒ Approve	☐ Approve as amended	☐ Disapprove	☐ No action

M. The P&T Committee voted unanimously to approve the recommendation that no brand single entity angiotensin-converting enzyme inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Deputy Commissioner	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Commissioner	☒ Approve	☐ Approve as amended	☐ Disapprove	☐ No action

N. The P&T Committee voted unanimously to approve the recommendation that no brand combination angiotensin-converting enzyme inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Deputy Commissioner	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Commissioner	☒ Approve	☐ Approve as amended	☐ Disapprove	☐ No action

O. The P&T Committee voted unanimously to approve the recommendation that no brand angiotensin II receptor blocker is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Deputy Commissioner ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Commissioner ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

P. The P&T Committee voted unanimously to approve the recommendation that no brand combination angiotensin II receptor antagonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Deputy Commissioner ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Commissioner ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Q. The P&T Committee voted unanimously to approve the recommendation that no brand mineralocorticoid (aldosterone) receptor antagonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Deputy Commissioner ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Commissioner ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

R. The P&T Committee voted unanimously to approve the recommendation that no brand combination mineralocorticoid (aldosterone) receptor antagonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Deputy Commissioner ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Commissioner ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

S. The P&T Committee voted unanimously to approve the recommendation that no brand single entity diuretic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Deputy Commissioner ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Commissioner ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

T. The P&T Committee voted unanimously to approve the recommendation that no brand combination diuretic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Deputy Commissioner ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Commissioner ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

U. The P&T Committee voted unanimously to approve the recommendation that no brand single entity potassium-sparing diuretic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Medical Director ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Deputy Commissioner ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Commissioner ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

V. The P&T Committee voted unanimously to approve the recommendation that no brand inhaled mometasone (Asmanex® Twisthaler®) is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Medical Director ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Deputy Commissioner ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Commissioner ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

W. The P&T Committee voted unanimously to approve the recommendation that no brand exenatide (Byetta®) is recommended for preferred status, regardless of cost.

Medical Director ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Deputy Commissioner ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

Commissioner ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action

X. The P&T Committee voted unanimously to approve the recommendation that no brand pramlintide (Symlin®) is recommended for preferred status, regardless of cost.

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐ No action

Respectfully submitted,

Nan Ferris

6/15/06

Nan Ferris, Pharm.D. **Date**